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REVIEWS

Importance of Epidemiology and Biostatistics in Deciding Clinical Strategies for Using Diagnostic Tests: A Simplified Approach Using Examples From Coronary Artery Disease

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The explosion of costly new medical diagnostic technologies demands a common sense approach to help physicians decide appropriate indications and strategies for use of these tests. This simple, nonmathematical review focuses on the assessment of coronary artery disease, but the approach can be generalized to other medical problems. This clinical approach to diagnostic testing strategies is based on seven sequential questions: 1. What is the clinical probability that this patient has a specific disease characteristic based on clinical data? 2. What is the overall objective for management of this patient based on the overall status of the patient? 3. Most importantly, what specific questions need to be answered about the patient's condition before the physician can recommend the most appropriate management (e.g., whether the patient has coronary disease, whether an anatomic lesion is functionally significant, whether a myocardial region is reversibly ischemic or irreversibly infarcted, whether a particular therapy has had good or bad effects or what is the patient's prognosis)? The key point is for the physician to formulate a specific clinical question about the patient before the test. 4. The physician must then ask how well does the test answer the particular clinical question about the patient. Here the physician needs to understand the sensitivity and specificity of the test, especially because they are influenced by various clinical biases. 5. Next, the physician must ask how to interpret the reliability of a positive or negative test result in the individual patient. This requires understanding predictive value and predictive error of a given result and how they are influenced by the clinical data as described by Bayes' theorem. 6. Next, the physician must ask what further tests or therapies will be recommended for the patient. The physician can estimate in advance how different test results would alter management plans and he can then allow this estimate to help determine indications for the test. There is some controversy concerning whether to use Bayes' theorem or multivariate analysis to estimate the final probability of a disease characteristic. 7. Finally, in this era of quality assurance, professional review and cost containment, it behooves each physician to ask whether the data provided by the particular tests were worth the cost, inconvenience and risk for that particular patient.

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A 35 year old personal friend calls you in considerable distress because his own physician has told him that he has a "positive stress test." You know that your friend has no symptoms and, on questioning, he has no risk factors. In addition, he regularly beats you in tennis. Your first question is, "Why on earth did anybody do a stress test on you, anyway?"

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The preceding anecdote brings up a question that is becoming increasingly important because of the widespread development and application of numerous expensive noninvasive tests to "screen" for coronary artery disease. Common sense and pressure from third party payers both indicate the need for physicians to develop a systematic approach to diagnostic test ordering. A rational approach to the use of noninvasive exercise tests in the overall management of people with known or suspected coronary artery disease can be developed on the basis of simple concepts of clinical epidemiology and biostatistics. Coronary artery disease is used here as an example, but the general approach to the problem can be readily extrapolated to tests in other areas of medicine. The approach offered here allows each physician to develop his or her own personal guidelines for using these

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Table 1. Clinical Approach to Use of Tests for Coronary Artery Disease

1. Make a clinical estimate of the probability of disease based on history, physical examination and preliminary laboratory tests.
2. Formulate options in further management.
3. Define the *specific question* that needs to be answered to decide among management options.
4. Define performance of tests available to answer the specific question (sensitivity and specificity).
5. Synthesize test results with preliminary clinical estimate to give best answer to the specific question (predictive value and error).
6. Determine which further tests or therapies are needed, on the basis of clinical data and initial test results.
7. Review whether the testing strategy used was optimal for each individual patient.

tests (Table 1) on the basis of individual responses to the seven questions presented in the text. Individual physicians should answer these questions somewhat differently to make their test ordering practices consistent with their view of the roles of surgery and angioplasty in coronary disease.

We have emphasized the use of tests to diagnose the presence or absence of coronary disease because clinical studies to date have provided the best data for that question. Finally, apologies must be offered to the serious statistician or epidemiologist because this review is designed to simplify this very complex but important area. We hope to introduce this important subject to new readers who could, then, read the more sophisticated, mathematically oriented reports in this field.

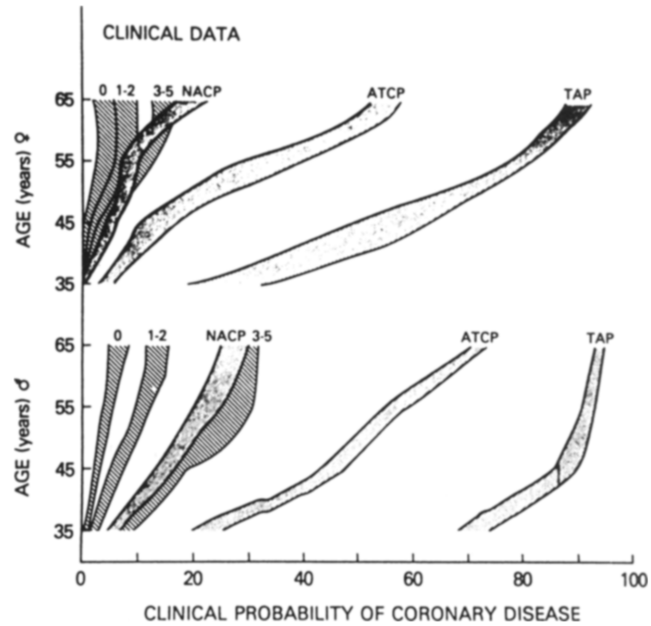


Figure 1. Use of clinical data to estimate the probability of coronary artery disease. Clinical data include gender (women are shown in the **upper panel**, men are shown in the **lower panel**), age (increasing up vertical axis), number of risk factors for asymptomatic people (0 to 5 of the following: diabetes, hyperlipidemia, hypertension, smoking and at rest electrocardiographic abnormality of ST-T waves). Symptoms are defined as nonanginal chest pain (NACP), atypical chest pain (ATCP) and typical angina pectoris (TAP). The probability of coronary artery disease increases from **left to right**, and the 95% confidence intervals are shown as the **widths of the bar**.

Question 1

What Is the Clinical Probability That This Patient Has Coronary Artery Disease or the Specific Disease Characteristic?

By assessing the patient's age, gender, number of risk factors (1–3) and specific characteristics of symptoms (4), it is possible to roughly estimate the probability of coronary artery disease. Figure 1 offers a convenient summary of the probability of coronary artery disease (5) predicted by simple clinical information cited in Tables 2 and 3. These data have been derived primarily from investigations such as the Framingham Study (1,2), which defined the incidence of new (first) coronary events over a 7 year follow-up period in a large community-based population, and from a summary of the probability of coronary disease based on chest pain reviewed by Diamond and Forrester (4). A more precise, linear relation with serum cholesterol was demonstrated by Stamler et al. (3), using a database of >356,000 patients studied prospectively. This *incidence* of new coronary events over 7 years correlates closely with the *prevalence* of coronary disease found on coronary arteriography at a single point in time (4). Although incidence (new events over time) is not the same as prevalence (disease present at one time), their rates are nearly identical in this circumstance (4).

This estimate of the likelihood of coronary artery disease before any test is performed is crucial, both for making further decisions on the need for tests (6,7) and for determining the final likelihood of coronary artery disease, based on a synthesis of clinical and exercise test data. All clinicians will recognize the approximate nature of this estimate be-

Table 2. Clinical Data Needed to Assess Risk Factors for Coronary Artery Disease

1. History of chest discomfort.
   - Provoked by exercise.
   - Located in center of chest.
   - Relieved after 2 to 10 min by rest.
2. History of smoking.
3. Physical examination—blood pressure.
4. Laboratory data—blood sugar.
5. Laboratory data—serum cholesterol.
6. Laboratory data—rest ECG.

ECG = electrocardiogram.

Table 3. Criteria to Classify Chest Discomfort (13)

Criteria
1. Precipitated by exercise.
2. Brief duration (2 to 15 min).
3. Relieved promptly by rest or nitroglycerin.
4. Substernal location.
5. Radiation from chest to jaw, left arm or neck.
6. Absence of other causes for pain.

Classification
- I. Typical angina pectoris
  - Criteria 1 to 3 all positive.
  - Any four criteria positive.
- II. Atypical chest pain
  - Any two criteria positive.
  - Only criteria 4 to 6 positive.
- III. Nonanginal chest pain
  - Only one criterion positive.

cause of the variability of the patient's history and the clinical assessment of risk factors.

Question 2

What Is the Overall Objective for Management of This Patient?

Although the objective for most patients would be to relieve symptoms if present and to prolong life if possible, objectives must be individualized for each person. The physician must consider the patient's age, life style, other medical conditions and the patient's attitude toward invasive therapies. In addition, each physician should make decisions about ordering tests that are consistent with his or her personal opinions regarding the safety and accuracy of the particular tests and therapies within the local medical community.

The physician's philosophy is of crucial importance in determining how strongly he or she needs to know the information available from each diagnostic test. For example, the physician who believes that coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty is useful only for patients who have disabling symptoms despite maximal medical therapy (8,9) should use a conservative approach in ordering tests that are unlikely to affect management. On the other hand, physicians who are convinced that coronary artery bypass surgery or coronary angioplasty can prolong life in most patients with coronary artery disease (10,11) should be aggressive in seeking evidence for coronary artery disease in their patients.

Similarly, the need to know whether coronary artery disease is present is dependent on individual patient characteristics. An obvious example is that the need to know might be very great in a 40 year old airline pilot with chest pain and not very great in a demented 85 year old cancer patient with typical angina. This need can only be determined if the patient's medical and social condition are thoroughly understood by the responsible physician. Thus, the need to know must influence the decision of whether to proceed with further diagnostic testing and, if so, which test to use.

Table 4. Indications for Tests: Examples of Specific Questions That Need to Be Answered About the Patient's Condition

1. Is coronary artery disease present or absent?
2. Is anatomic coronary stenosis observed on angiography physiologically significant?
3. What is the patient's prognosis?
4. Are there regions of viable but potentially ischemic myocardium in the patient's heart after a myocardial infarction?
5. What is the patient's response to a particular therapeutic intervention?

Question 3

What Specific Questions Need to Be Answered About the Patient's Condition Before the Physician Can Recommend the Most Appropriate Management (Table 4)?

The physician must formulate one or more specific clinical questions that need to be answered when referring a patient for a test. The questions should evolve from the overall goal of clinical management to provide focus and organization to the evaluation. There are several possible questions (Table 4). The present review focuses on the first question because the best data are available to determine the presence or absence of coronary artery disease from noninvasive studies.

Most of the newer technologies, such as nuclear cardiology tests, have been assessed by comparing their ability to identify the presence or absence of coronary artery disease (12,13) or to identify patients with high risk coronary anatomy (14,15) using coronary angiography as the reference or "gold" standard method. There are other, potentially more important clinical questions that need to be answered. For example, the ability of these tests to assess the functional significance of a lesion observed on coronary angiography is only partially defined. One must be aware that the reliability of an estimate of whether a lesion is significant may be lower than the reliability of a prediction of the presence or absence of coronary artery disease. Also, the physician might want to assess differences in coronary collateral perfusion distal to similar anatomic lesions (16,17). The most meaningful way to define the significance of an anatomic lesion may be to define the impact of the lesion on the patient's prognosis.

In recent years, several centers (18–24) have presented data concerning the ability of exercise stress tests to predict prognosis. Because cardiac events such as death or new myocardial infarction occur with a relatively low frequency, long-term follow-up study of large numbers of patients is required. The natural history of the disease is now frequently

Table 5. Definitions of Sensitivity, Specificity, Predictive Value and Predictive Error (based on a two by two table)

	Disease Present	Disease Absent	Totals
Test positive	True positive	False positive	All positive tests
Test negative	False negative	True negative	All negative tests
Total	All with disease	All with no disease	All patients tested

altered by surgery or angioplasty. For these reasons, the ability of a noninvasive stress test to predict prognosis is less easily defined than the ability to identify the presence or absence of coronary artery disease.

In trying to decide whether to recommend invasive interventions such as bypass surgery or angioplasty for a patient with prior myocardial infarction, it is essential to distinguish infarction from ischemia because interventions can only help ischemia. The best clinical technique that is widely available for this purpose is observing redistribution to fill in a defect from stress to delay images on thallium-201 imaging (12).

Once the variability of individual tests is understood, assessing the response to therapy may be one of the best uses of these tests because one can compare the test in the same patient at different points in time (25–28). Once the physician formulates a clear clinical question for the patient's management, it is relatively easy to decide which tests will contribute information useful for clinical decision-making.

Question 4

How Well Does the Test Answer the Particular Clinical Question About the Patient?

Test performance is best described by statistical expressions of sensitivity and specificity (Table 5, Fig. 2). These two statistical expressions must be defined for each particular test in a group of patients who are known by some independent reference method to have or not have the characteristic for which testing is performed.

Sensitivity is defined as the probability that the test will be positive in a group of patients who are known to have coronary artery disease by an independent method such as coronary angiography. Stated another way, sensitivity is the percent of patients with disease who can be identified by a positive test (29,30).

Specificity is defined as the probability that the test will be negative in a group of patients known *not* to have coronary artery disease by angiography. Stated another way, specificity is the percent of patients who do not have coronary artery disease who can be identified correctly by a negative test (29,30). Sensitivity and specificity can also be calculated to define the ability of tests to define characteristics such as

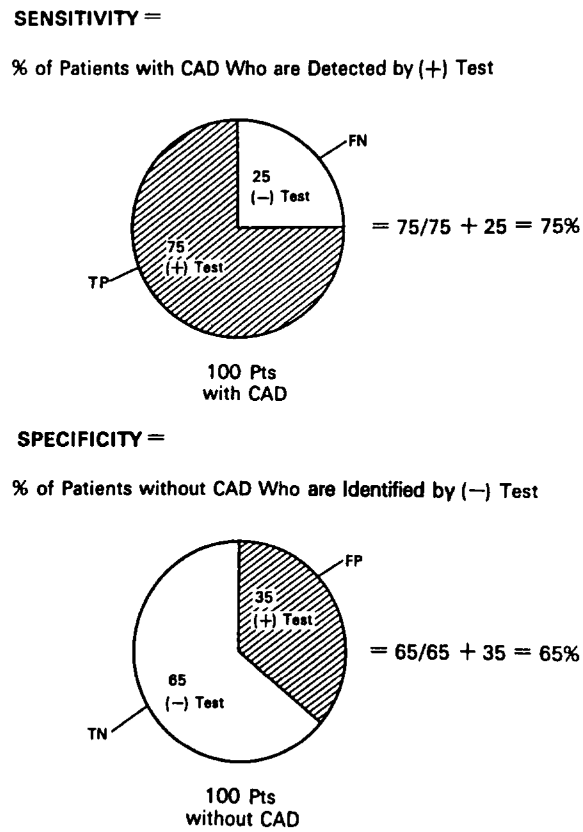


Figure 2. Pie diagrams show definitions of sensitivity and specificity in hypothetical groups of 100 people known to have coronary artery disease (CAD) by coronary angiography (sensitivity, **above**) or of 100 people known not to have coronary disease (specificity, **below**). These hypothetical values are for exercise electrocardiography. F = false; N = negative; P = positive; T = true; + = positive test; − = negative test.

the presence or absence of a coronary event during the follow-up period.

Published values of sensitivity and specificity for various noninvasive tests may not always agree with local clinical experience because of a variety of factors that can influence these variables of test accuracy.

Nondiagnostic tests. One reason that published values of sensitivity and specificity may differ is the method chosen to deal with patients who have nondiagnostic test results. Nondiagnostic results can occur in 30% to 40% of patients having an exercise electrocardiogram (ECG) (13). If patients with a nondiagnostic test are excluded in the calculation of sensitivity or specificity, test accuracy will be inflated (Fig. 3). Thus, one factor to search for in published reports of sensitivity and specificity of a test is the way the authors chose to deal with nondiagnostic test results (13).

Criteria for a positive test. Another factor that causes major differences in sensitivity and specificity values is the choice of criteria to interpret a test as positive or negative (Fig. 4 and 5) (29,31). For example, if an exercise ECG is

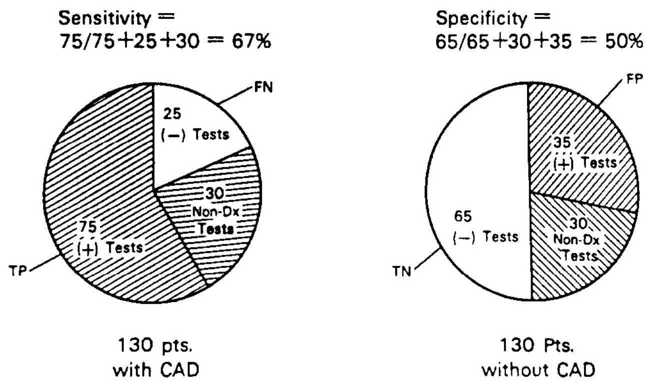
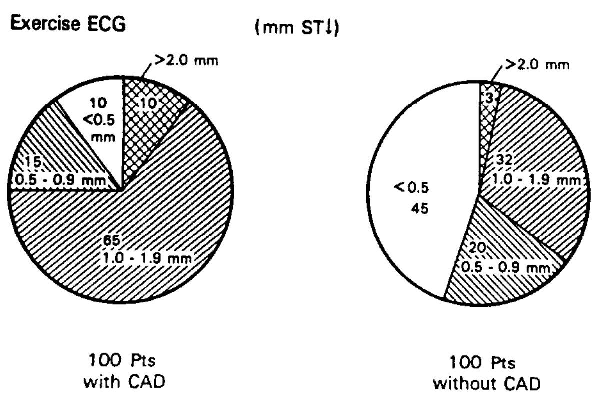


Figure 3. Effect of including nondiagnostic (non-DX) tests on the calculated sensitivity and specificity of exercise electrocardiography in the same study group as in Figure 2. Note that adding 30 patients with a nondiagnostic test to the denominator decreases both sensitivity and specificity. Sensitivity and specificity are worse when including non-DX tests. + = positive test; − = negative test; other abbreviations as in Figure 2.

read as positive when a patient has >0.1 mV (1 mm) flat depression of the ST segment, then the sensitivity might be 75% and the specificity 65%. If the same exercise ECG is read with a new criterion of >0.05 mV (0.5 mm) flat ST segment as positive, then more patients with disease would have a "positive" test. Thus, the sensitivity of the test would increase. Unfortunately, lowering the criterion for reading a test as positive also influences specificity (31). Because a larger proportion of all tests will now be interpreted as positive (including those of patients without disease), the specificity will decrease. Similarly, if one requires that the exercise ECG show the stricter criterion of >0.2 mV

Figure 4. Effect of changing the criterion for reading a test as positive (+), using as an example the number of mm ST segment depression on electrocardiography (ECG) during exercise (0.1 mV/mm). This pie diagram shows the hypothetical distribution of ST depression in the 100 people from Figure 3 with known coronary artery disease (CAD). On the **right** is a diagram for the 100 people without disease. These data are used to recalculate sensitivity and specificity, using different criteria for the number of mm of ST depression required to call the test positive.



Criterion for (+) ST	Sensitivity	Specificity
≥ 2.0 mm	10%	97%
≥ 1.0 mm	75%	65%
≥ 0.5 mm	90%	45%

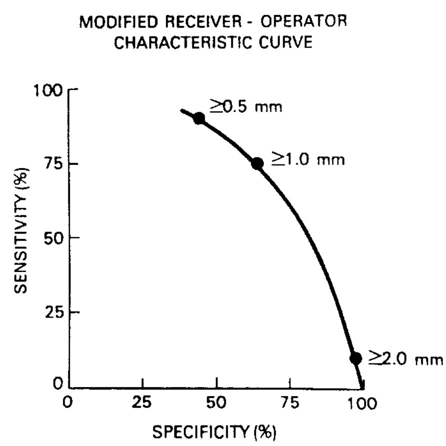


Figure 5. Effect of changing criterion for positive (+) test. Data in Figure 4 were used to construct a modified receiver-operator characteristic (ROC) curve showing the inverse relation between sensitivity and specificity. As the criterion for interpreting the ST depression as positive changes from 0.5 to 1.0 to 2.0 mm, the sensitivity decreases but specificity increases. The curve is plotted here as true positive rate (sensitivity) versus specificity for clarity, but is usually plotted as true positive rate (sensitivity) versus false positive rate (1 − specificity).

(2.0 mm) ST segment depression to be read as positive, then fewer patients with disease will have a positive test and the sensitivity will be much lower. In addition, fewer patients without disease will have a positive test, so specificity will be much higher (29,31).

This example illustrates the point that the physician cannot "get something for nothing" in test accuracy simply by changing the criteria for reading the same test data. This trade-off is called a receiver-operator characteristic (ROC) curve when expressed graphically (29,31) (Fig. 5). Changing criteria to increase sensitivity will decrease specificity and, similarly, changing criteria to increase specificity will decrease sensitivity. The same considerations apply to criteria for interpreting any type of test in any area of medicine.

Patient selection (Fig. 6). The sensitivity and specificity of a test are assumed not to be influenced by changes in the prevalence of disease in the group of patients being tested if the patients represent a randomly selected group (4,29,32,33). On the other hand, if the group of patients tested is influenced by some selection factor, there may be systematic changes in sensitivity and specificity. For example, it is common medical practice to select patients for cardiac catheterization because of a positive noninvasive stress test. For this reason, specificity (probability of a

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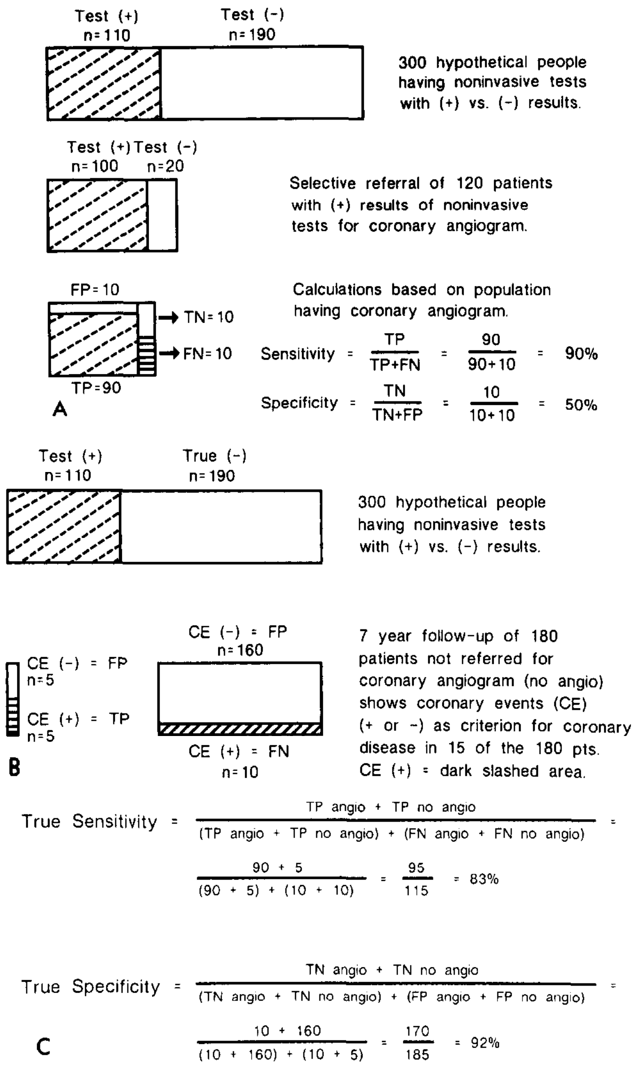


Figure 6. Hypothetical illustration of the effects of selecting patients from the group undergoing coronary angiography in order to calculate sensitivity and specificity. **Panel A**, Group selected for angiography to define the prevalence (presence or absence) of coronary artery disease. The **top bar** shows all 300 hypothetical people having non invasive tests and the **middle bar** shows the 120 people who were referred for angiography. The **bottom bar** shows how these 120 angiographic results were used to calculate sensitivity and specificity based on the angiographic results to establish true (T) versus false (F) positive (P) or negative (N). Because there is selective referral to angiography of patients with a positive noninvasive test, the sensitivity is high and the specificity is low. **Panel B**, Data for all patients, including those not referred for angiography. The **top bar** shows all 300 hypothetical people having noninvasive tests and the **middle bar** shows the 180 patients who were not referred for angiography (angio). If these patients are followed for 7 years to determine the incidence of coronary artery disease (which corresponds to prevalence in this instance), all patients could be grouped into those with versus without disease. Considering all patients, including those not referred for angiography, decreases sensitivity slightly and increases specificity relative to the group selected for angiography. **Panel C**, Calculation of true sensitivity and specificity based on all patients, where results for patients with and without angiography are added. Thus, true sensitivity and true specificity can be recalculated using all 300 people referred for noninvasive tests. Abbreviations as in Figure 2.

negative test in a person without disease) is usually lower in patients selected from a group already referred for cardiac catheterization than in normal volunteers without symptoms (13). One possible explanation is that some patients with a positive noninvasive test but normal coronary arteries may have disease detectable by noninvasive tests for myocardial dysfunction but not by angiography of large vessels and rest ventriculography (34).

Our group (13) was one of the first to note the impact of selection bias on the accuracy of the noninvasive diagnosis of coronary artery disease. We noted that at one institution the proportion of cardiac catheterization studies performed for chest pain that revealed normal coronary arteries decreased from 30% in 1976 (before) to 10% in 1978 (after, when thallium imaging results were used to select patients for catheterization). On the one hand, these findings suggest that thallium-201 imaging is clinically useful because many patients with negative myocardial imaging results were no longer being referred for coronary angiography. The other effect of this trend, however, is that many of the people who would have had true negative thallium-201 images, thereby maintaining specificity of the technique (as defined by cardiac catheterization), were systematically excluded from the cardiac catheterization laboratory. Indeed, the specificity of exercise thallium-201 imaging also decreased (from 100% to 74%) as the test became more readily accepted as a screening tool for catheterization (13). Thus, selective referral of people with a positive test both decreases the rate of detection of true negative results and increases the rate of detection of false positive results in the group, resulting in reduced specificity.

Selection bias could also artificially increase the sensitivity by excluding people with a false negative noninvasive test from the cardiac catheterization laboratory. In our study group described previously (13), the 40 month prognosis was excellent for patients with a negative exercise thallium test and no cardiac catheterization (22), thus supporting the validity of the decision not to perform angiography after a negative thallium test. This effect of selection bias was discussed at greater length in a report (35) of a declining specificity of gated blood pool scintigraphy. Thus, intrinsic bias in patient selection can profoundly influence calculated test accuracy (36).

Biased interpretation. Another important question that can influence the sensitivity and specificity is whether the physician interpreting the test knows clinical information about the patient *before* interpreting the test data. Such prior knowledge may create serious bias for the physician interpreting the test (4,29). We use and strongly suggest the following approach for physicians who read tests (for example, nuclear cardiology specialists). Readers should initially interpret the images without any knowledge of the patient's age, clinical status or exercise test data and commit themselves in writing to an impression to avoid bias. In this way, both the referring clinician and the nuclear cardiology

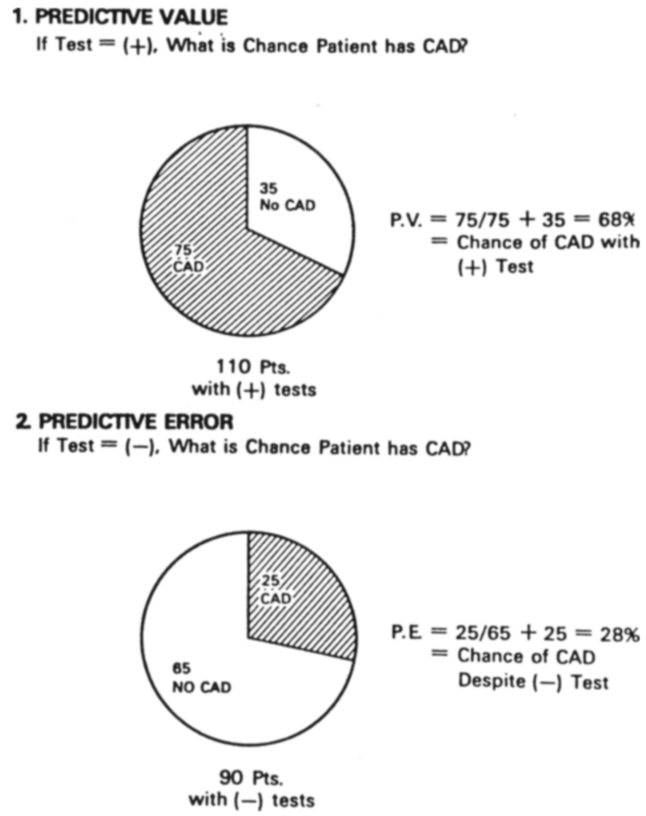


Figure 7. Definitions of predictive value and predictive error in the 110 patients (Pts.) with positive test from Figure 2 (predictive value [P.V.], **above**) or of the 90 people with a negative test from Figure 2 (predictive error [P.E.], **below**). The term negative predictive value is sometimes used for 1-predictive error. Abbreviations as in Figure 2.

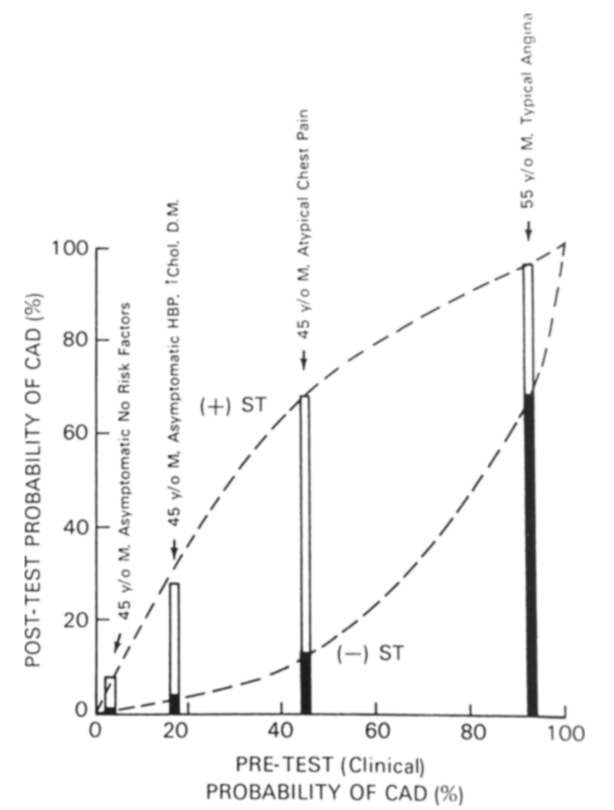


Figure 8. Use of Bayes' theorem to calculate the probability of coronary artery disease (CAD). Clinical data (pretest probability, increasing from **left to right**) are combined with results of exercise electrocardiography (positive [+] or negative [−] ST segment response) to yield final posttest probability (increasing along the **vertical axis**). Four specific patient examples are shown by **vertical bars**, where the height of the **solid dark bar** shows the results for a negative exercise electrocardiogram (ECG) (−) ST, and the **clear bar** shows the results for a positive exercise ECG (+) ST. The patient shown on the **far left** has a very low (1% to 4%) probability of coronary artery disease from Figure 1: (that is, a 45 year old [y/o] man [m] with no symptoms or risk factors). The second patient has a low (15% to 18%) probability of coronary artery disease; (that is, a 45 year old man who is asymptomatic but has three risk factors: high blood pressure [HBP], hypercholesterolemia [chol.] and diabetes mellitus [D.M.]). The third patient has an intermediate (42 to 47%) probability of coronary artery disease (that is, a 45 year old man with atypical chest pain), and the fourth patient has a high (89% to 92%) probability of coronary artery disease (that is, a 55 year old man with typical angina pectoris). In patients with a diagnostic test the sensitivity was 0.84 and specificity was 0.62. Although a positive exercise ECG always increased the probability of coronary artery disease above that found with a negative test, the posttest or final probability of coronary artery disease increased dramatically when the clinical picture suggested a higher pretest probability of disease.

specialist can offer truly independent opinions. Next, the reader and the referring physician can synthesize the results of clinical information (Fig. 1) and the noninvasive test (Fig. 7) to make a final estimate of the probability of coronary artery disease (Fig. 8). The final nuclear cardiology report should then offer a conclusion that takes into account the clinical data. This conclusion might include an alternative interpretation of the scan, just as long as it is clearly labeled as being influenced by clinical data (for example, "in light of the clinical history of a 60% reduction in diameter of the left anterior descending coronary artery, the mild decrease in thallium-201 activity in the anterior wall may be physiologically significant"). When the nuclear cardiology specialist, however honest and well meaning, makes an initial interpretation of the images with full knowledge of the patient's clinical information, the patient may be deprived of two truly independent opinions.

To summarize, it is important that the physician referring a patient for a test know the sensitivity and specificity of the test in his or her community to answer the question being posed. Only in this way can the physician judge the reliability of the information received from the test in guiding future management of the patient.

Question 5

How Can the Physician Interpret the Reliability of a Positive or Negative Test Result in the Individual Patient?

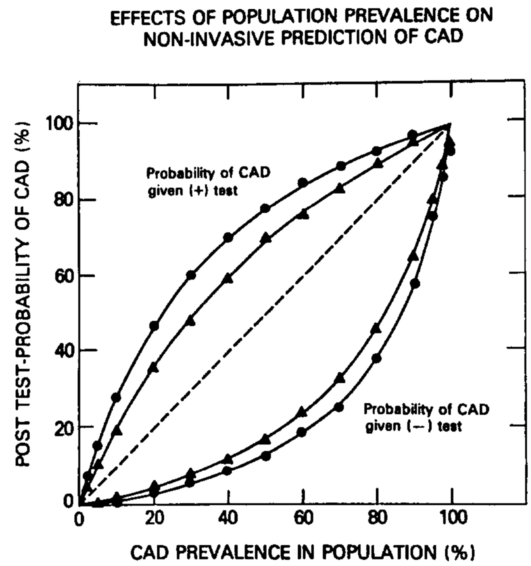
This question is more directly relevant to the care of particular patients than was the previous question about test performance. To interpret the meaning of a specific positive test, one needs to know the predictive value of the test (Fig. 7). Predictive value is defined as the probability that a patient with a positive test actually has coronary artery disease. Stated differently, the predictive value is the chance that a positive test is correct in identifying coronary disease (4,29,30,32,33). On the other hand, predictive error is the probability that a person with a negative test actually does have coronary disease. The predictive error is the chance that a negative test is wrong (4,29,32,33). Another commonly used term is negative predictive value, which is 1.0−predictive error.

Bayes' theorem. Both predictive value and predictive error are higher in populations in which the prevalence of coronary artery disease is higher (4,29,30,32,36). It makes sense that in a group of patients with a higher clinical or pretest probability of coronary disease there would be a greater chance of an individual patient having such disease whether the test is positive (predictive value) or negative (predictive error). This is the basic message of Bayes' theorem, as shown in Figures 8 and 9 (4,13,29,30,32,33).

Two clinical examples to illustrate these issues of predictive value and predictive error, as described by Bayes' theorem, are simply expressing common sense or good clinical judgment. As indicated in Figure 1, a 55 year old man with a history typical of angina pectoris has a 90% to 95% chance of having coronary artery disease on the basis of clinical information alone. In contrast, a 35 year old woman without symptoms or risk factors has only a 0.5% to 1.5% chance based on clinical information alone. Thus, even if the 55 year old man with typical angina has a negative exercise ECG and the 35 year old woman without symptoms has a positive test, the experienced clinician's estimate of the probability of coronary artery disease would not be significantly influenced by test results.

Figure 8 shows the graph obtained by substituting these values of sensitivity and specificity in the equation for Bayes' theorem (13). If the 55 year old man has a negative exercise ECG, his chance of having coronary artery disease is still 40% to 50%, whereas the 35 year old woman with a positive exercise ECG has only a 2% to 4% chance of having this disease. In general, as the pretest probability of coronary disease (based on clinical information) increases along the horizontal axis, the chance of having coronary disease after the test result increases along the vertical axis. Because predictive value and predictive error depend critically on the prevalence of disease in the group under study, it is meaningless to report predictive value or error without specifying the disease prevalence in that group. In fact, because prevalence of disease in different patient populations can vary over a wider range (0.1% to 99.9%) than sensitivity or specificity of clinically useful tests (50% to 95%), one can conclude that prevalence is the most important factor influencing predictive value and error (36). Thus, we strongly recommend a subscript indicating disease prevalence below any published report of predictive value or error.

Patients with a positive test are described by the curve in the upper left of Figure 8, which is always higher than the curve in the lower right for patients with a negative test. Figure 8 also shows that if a test is more accurate than another (for example, radionuclide scintigraphy versus exercise ECG) then the chance of having coronary artery disease will be higher for any patient who has positive findings on the more accurate test than for a patient who has positive findings on the less accurate test (13,32,33). On the



Tests	Code	Non-Dx Test	Sensitivity (Dx-Tests)	Specificity (Dx-Tests)
E_xECG	▲—▲	35	84%	62%
201Tl	●—●	9	88%	74%

Figure 9. Graphic display of Bayes' theorem. As the pretest probability (or population disease prevalence) of coronary artery disease (CAD) increases from **left to right** along the **horizontal axis**, the posttest probability of disease increases along the **vertical axis**. The chance of coronary disease is greater at any prevalence if the test is positive (predictive value, **upper left curves**) than if the test is negative (predictive error, **lower right curves**). The **diagonal broken straight line** going up from **left to right** shows the probability of disease in patients with nondiagnostic test results. These curves were calculated from the equations for Bayes' theorem shown in the text, using the values of sensitivity (75%) and specificity (65%) for exercise electrocardiography (E_x ECG), excluding patients with a nondiagnostic (non-DX) test.

other hand, if the specificity and sensitivity are higher, the chance that patient with a negative radionuclide study has coronary disease is less than that of a patient with a negative stress ECG.

The equations for Bayes' theorem are quite simple and intuitively reasonable (4,13,29,30,32,33). The probability of coronary artery disease in a patient with a positive test (predictive value) is related to test accuracy and the chance that disease is present in the group of patients having the test, as follows:

$$\text{True positives}/(\text{True positives} + \text{false positives}).$$

This equation is equivalent to:

$$\frac{(\text{Sensitivity})\,(\text{Prevalence})}{(\text{Sensitivity})\,(\text{Prevalence}) + (1-\text{Specificity})\,(1-\text{Prevalance})}.$$

On the other hand, the probability of coronary artery disease in a patient with a negative test (predictive error) is:

$$\frac{\text{False negatives}}{\text{False negatives} + \text{True negatives}}.$$

This expression is equivalent to:

$$\frac{(1-\text{Sensitivity})\,(\text{Prevalance})}{(1-\text{Sensitivity})\,(\text{Prevalence}) + (\text{Specificity})\,(1-\text{Prevalence})}.$$

Some authors report negative predictive value that is 1−predictive error or:

$$\frac{\text{True negatives}}{\text{False negatives} + \text{True negatives}}.$$

If the sensitivity and specificity of the test are known and the clinical data allow an estimate of the prevalence of coronary artery disease for the patient in question, the physician can calculate the chance that the patient has coronary disease on the basis of clinical information and a particular positive or negative test result (Fig. 7 and 8). If the sensitivity and specificity of tests are similar to those used in Figures 7 and 8, one can simply draw a vertical line from a point on the horizontal axis, where the patient data fit the prevalence of disease in the group, up to either the negative or the positive curve on the graph.

An important clinical issue is what level of post-test probability is required to rule in or rule out coronary artery disease for an individual patient. A frequently used threshold is 5%, but this level could and should be varied to suit the clinical situation, as indicated in the next section (Question 6). For some patients, the clinician would require the probability to be <2% to 3% to rule out coronary artery disease (for example, in a 40 year old airline pilot), whereas for others, 10% to 15% might be acceptable (for example, in a 70 year old cancer patient). The main aim in estimating a probability of disease is to avoid an oversimplified diagnosis of disease from the test. On the basis of probability, the physician can decide what, if any, steps should be recommended.

Bayes's theorem is, indeed, clinically useful because it allows the physician to estimate the significance of a particular positive, negative or nondiagnostic test result in the individual patient. This decision concerning the probability of disease based on the integration of clinical and laboratory data is a crucial step that must precede any decision about further management.

Question 6

What Further Tests or Therapies Will the Physician Recommend for the Patient?

The physician must actually ask this question *before* ordering the test. In this way, one can avoid the situation mentioned in the anecdote about the hypothetical 35 year old personal friend with a positive stress test. In other words, if the management plan would not change on the basis of a particular test result, the physician must ask whether the test would have any value (33). If the physician knows in advance that the management plan would not be changed by a positive or negative test result, the test is probably unnecessary.

Another question to ask after the initial results are obtained is whether additional tests would be useful to help decide further management (Fig. 9). The physician can use Bayes' theorem again by taking the patient's pretest probability of having coronary artery disease and recalculating it after the result of a first test is known. For example, with use of the exercise ECG, the revised probability of having disease can be substituted on the horizontal axis of Figure 8 as the pretest probability with a radionuclide scintigram (5,33). In this way, the physician can assess whether performing radionuclide imaging after the results of the exercise ECG are known would provide a useful increment in information about the patient.

Patient examples. As an example, neither a 35 year old woman without symptoms nor a 55 year old man with typical angina would likely benefit from an additional test such as radionuclide imaging, whatever the results of the stress ECG (5). The woman without symptoms has such a low probability of having disease that it would be changed only minimally by further testing. An important exception would be the use of exercise radionuclide testing instead of cardiac catheterization to reassure an anxious patient (or insurance company) that the positive exercise ECG does not mean that coronary artery disease is present.

On the other hand, the probability that a 55 year old man with angina has coronary disease is so high that a negative exercise ECG reduces it only to 40% to 50%, which is not a clinically very useful difference (5). In contrast, if the woman were 45 instead of 35 years old and had atypical chest pain, her chance of having coronary artery disease before any test would be about 15% (Fig. 1) (1,2,4). If she then had a positive stress ECG, her chance of having coronary disease would be about 25% to 30% (Fig. 8). For a patient in this situation, performing radionuclide scintigraphy would be most useful. If radionuclide imaging results were negative, her chance of having coronary disease would be reduced to 2% to 4%, a probability that would be quite useful clinically to stop the diagnostic evaluation and reassure the patient (5). Once again, these numeric values were simply read sequentially from Figures 1 and 8. The physician could not justify reassuring the 55 year old man with typical angina even if both noninvasive tests were negative, whereas the 35 year old woman without symptoms would have such a low probability of having disease that a change in management with a positive test result would be unlikely.

Here again, the physician's opinion about the role of coronary surgery or angioplasty in improving longevity of patients with coronary artery disease plays an important role in test utilization. The physician who thinks that surgery substantially prolongs life in a large number of patients with coronary disease, should be quite aggressive in seeking to identify these patients. This aggressive approach and strong need to know might even lead the physician to recommend coronary angiography directly, rather than ordering noninvasive tests in patients when clinical information already suggests a moderate to high probability of coronary disease. On the other hand, a physician who is conservative and not convinced that coronary surgery is necessary in the vast majority of patients might use noninvasive testing more to identify high risk patients than to diagnose the presence of coronary artery disease or might use it as a guide for medical therapy. For example, a physician seeing an elderly patient on medical therapy for a presumed diagnosis of coronary disease might order a noninvasive test to rule out disease and allow stopping medications and avoiding future hospital admissions. The physician should have a clear objective and be consistent in applying his or her view of invasive therapies to the utilization of diagnostic tests.

Statistical controversy (Table 6). There is some controversy concerning the usefulness of Bayes' theorem as just described (37,38). It is assumed in Bayes' theorem that the pretest clinical estimate of the probability of disease is conditionally independent of the results of the test itself (5,36–38). For example, the exercise ECG result should not depend on the clinical data. In one sense, they are not independent because a group of 55 year old men with typical angina and a 90% to 95% clinical probability of having coronary artery disease would also have a high probability of having a positive exercise ECG. Thus, these two separate types of data are not entirely independent in the sense that both clinical data and exercise test results would reveal physiologic consequences of coronary disease. Similarly, a group of 45 year old men with no symptoms or risk factors and a 3% clinical probability of having coronary disease would have a low probability of having a positive exercise ECG. One could argue that the clinical information is only related to the results of the noninvasive test because both provide assessments of the probability of coronary disease in the same group, assuming that the clinical information is not made known to the person interpreting the noninvasive test. The fact that a positive noninvasive test result is more likely in a patient whose clinical information also indicates a high probability of having coronary disease does pose a theoretical objection to this application of Bayes' theorem (36–38).

Similarly, in one study (38), patients with a positive exercise ECG had a higher likelihood of positive exercise radionuclide imaging than did patients with a negative exercise ECG. If the total number of tests is small (fewer than five to eight), the violation of the assumption of independent predictions would not cause significant problems (39). Furthermore, Bayesian schemes have been validated to estimate the final probability of coronary artery disease from clinical information and serial noninvasive test results (40). In a population of >1,000 patients, noninvasive predictions of coronary disease using Bayes' theorem and serial tests correlated closely with actual prevalence of disease (40).

A second question concerning the use of Bayes' theorem to diagnose coronary artery disease is whether the sensitivity and specificity of a test remain the same in different groups (36,37). Some data suggest that the sensitivity and specificity of the exercise treadmill test vary in groups with different prevalences of disease. For example, a sensitivity of 22% for the exercise ECG to detect coronary artery disease has been observed (41) in a group of relatively young women with "nonischemic chest pain." That low sensitivity, however, represented only two of nine patients. The sensitivity in this group with a 5% prevalence rate of disease was lower than that in the group as a whole (76%). In another exercise ECG study (42), sensitivity varied according to maximal exercise heart rate, number of diseased coronary arteries, type of chest pain, age and gender; specificity varied with maximal exercise heart rate. Hlatky et al. (42) concluded from these results that the assumption of constant values of sensitivity and specificity for Bayes' theorem may be adequate for individual patient estimates in which the pretest probability of disease is always uncertain. In decision and cost-benefit analyses, however, these authors (42) indicated that the assumption of a constant sensitivity and specificity could lead to erroneous conclusions.

Diamond (43) indicated that the results of this study by Hlatky et al. (42) could be explained by bias in selecting patients for cardiac catheterization based on a positive noninvasive test. Indeed, Diamond (43) plotted the data from the study by Hlatky et al. to indicate that 63% of the variation in sensitivity and specificity was explained by

Bayes's theorem and selection bias. He offered a mathematical approach to correcting the Bayesian estimates of disease probability for selection bias based on the total number of positive and negative tests in the population. One should note that the study by Hlatky et al. (42) does not seem to offer blinded readings of the exercise ECG and, as indicated above, this potential observer bias might contribute to the higher sensitivity observed in men with typical angina, older age and lower maximal exercise heart rate. The study by Hlatky et al. (42) may not have avoided observer bias but still provides useful information and concepts. Thus, the statistical assumptions in Bayes' theorem may not apply to all clinical studies such as these where study patients were not chosen at random. In fact, the validation studies just cited (38–40) suggests that the use of Bayes' theorem is clinically useful in randomly selected groups of patients.

Multivariate analysis. The alternative statistical approach is multivariate or discriminant function analysis, using a large group of real patients to establish a reference data base of patients undergoing cardiac catheterization (Table 4) (44, 45). Multivariate analysis offers the potential advantage that it may not assume the tests are independent of each other or that the sensitivity and specificity remain constant over a wide range of disease prevalence rates. Multivariate analysis to predict coronary artery disease, however, depends critically on how patients were selected to establish the reference data base. Thus, one might only be able to make reliable predictions in a group of patients similar to those referred for cardiac catheterization to the same institution at the time when the reference data base was being established.

Reliability of probability estimate. It must be emphasized that the clinician can only *estimate* the probability of coronary artery disease, and there is a considerable margin of error using either Bayes' theorem or multivariate analysis. When one understands that only an estimate can be achieved by the use of clinical and exercise test data, the potential differences between the use of Bayes' theorem compared with multivariate analysis become small. Diamond and Forrester (46) have emphasized the important and useful difference between the probability of coronary disease that is estimated versus the confidence that the physician has in that estimate of probability. Thus, one particular use of noninvasive testing is to validate the physician's clinical estimate of the probability of coronary disease. In reality, many patients do not present a reliable history that allows the physician to define precisely his or her clinical or pretest probability of coronary disease. Such patients can be represented on the graphs as having a broad range of clinical probabilities of coronary disease (Fig. 7 and 8).

For example, on one office visit, a patient may give a history typical of angina pectoris (induced by effort, relieved promptly by rest), but on the next visit, the patient may relate a different history of nonanginal chest discomfort (not related to exercise, lasting only seconds). In such patients, it will be useful to observe the response of their symptoms to exercise in the laboratory, as well as to use the ECG or radionuclide imaging data, or both, to define more narrowly the appropriate ranges of probability of coronary artery disease. Exercise testing is often performed in patients with an apparently high likelihood of having coronary disease based on clinical information. One must be cautious in concluding that this is always a waste of resources. The physician obtaining the clinical data will have the best perspective on how "soft" and potentially unreliable are the clinical data used to estimate the probability of disease in that individual patient. An objective test that confirms a very high or very low probability of coronary disease is very useful to the clinician—not only to change the estimate of the likelihood of disease—but also to increase his or her confidence that the estimate of coronary disease is correct. Also, in patients with a vested interest in the test result (for example, airline pilots on the one hand, and disability applicants on the other), noninvasive exercise tests may be quite useful as objective evidence for or against coronary disease to compare with the subjective history. In addition, there are numerous causes for a false positive clinical history (for example, musculoskeletal and cervical root pain) and a false negative history (for example, silent ischemia). Finally, the physician may order a stress radionuclide test in a patient with typical angina to assess prognosis and help decide whether or not the patient might benefit from coronary angiography.

In summary, an important concept for the physician to keep in mind is that a noninvasive test result provides a better estimate of the probability of coronary disease if clinical information is also taken into consideration after objective test interpretation. Whether clinical data are combined with noninvasive tests using Bayes' theorem or multivariate analysis is of secondary importance (Table 6). The relative simplicity of understanding Bayes' theorem (4,29,30,32,33,36) and using a nomogram (5) for its application offers certain practical advantages over the possibly more precise but more complex multivariate analysis.

Question 7

On Review of the Patient's Situation, Were the Data Provided by the Particular Test or Tests Worth the Cost, Inconvenience and Risk for the Patient? Might Another Testing Strategy Have Provided Better Information?

With this case by case self-assessment, the physician can continue to learn from personal experience. It is a useful goal in managing patients to try to limit the utilization of resources without compromising care, whether this involves the treadmill in one's own office or in the nuclear cardiology department of a hospital (47). Third party payers and government are currently watching closely as the cost of health care increases to >10% of the gross national product, and the care of patients with heart disease is >10% of the total cost of health care (30). Performing no tests or less expensive tests does not always minimize the overall outlay of health care resources for a patient because, for example, exercise thallium imaging may ultimately save the financial and other consequences of false negative and false positive results of the less accurate exercise ECG (47). Thus, cost-effectiveness (defined as cost per effect of the test on quality and quantity of life) appears to be better for exercise thallium-201 than for the exercise ECG (47). Sometimes additional tests are needed to provide incremental information, as shown for the exercise ECG, in addition to clinical information (Fig. 8) and for exercise thallium-201 imaging in addition to the exercise ECG (Fig. 9). This concept of gaining incremental information from additional tests is discussed in more detail in the preceding section (Question 6). It is possible to estimate the cost of this incremental information available from the additional test (47). Such considerations should be entertained by the physician as he or she discusses further testing with the patient. It is clear that more studies are needed to clarify the most economic use of health care resources, taking into account long-term consequences of erroneous test results and their complications.

Conclusions (Table 1)

Noninvasive exercise tests for coronary artery disease are imperfect, and the information they provide is <100% reliable despite attempts at quantification (48). The imperfection of the tests is the rationale for developing an approach such as the one described here. The seven questions proposed may help physicians determine their individual guidelines for the use of particular tests in evaluating patients with potential coronary artery disease. The main issue in deciding the indications and usefulness of a noninvasive test is whether that test or another test will influence the physician's actions or recommendations for further management. If the physician's management would not be changed by a positive or negative test result, the indications for the test would be considered weak. On the other hand, the greater the change in management that would be effected by a positive or negative result, the stronger are the indications for the test (33). Often a low probability of coronary disease could be reduced to <5% by a negative test, and even a small change in the likelihood of coronary disease to <5% would allow the physician to avoid additional tests to rule out coronary artery disease or a high risk anatomic situation (9–13). In this way, even a small change in probabilities might be very useful clinically. Patients to whom this situation would apply can be identified in advance by their having a relatively low clinical probability of coronary disease. By estimating their probability of disease by clinical information alone, and placing this on the horizontal axis of the graph of Bayes' theorem in Figure 7, one can estimate the potential usefulness of a negative noninvasive exercise test. Bayes's theorem simply provides a theoretical framework to combine the sensitivity and specificity of a noninvasive test with the clinical prediction of the probability of disease before the test to arrive at a more accurate final prediction of the chance of coronary disease. In a simplistic way, Bayes' theorem represents a mathematical model for good clinical judgment (5).

One could argue that under Question 2 an important management objective should be good care while expending only a reasonable amount of health care resources (47). This is a difficult goal for the cardiologist faced by a vast array of new technology. Even if a patient is wealthy and can afford to pay for the test, the facilities for performing nuclear cardiology tests, for example, may be overburdened by patients with marginal indications, causing long delays in obtaining tests that are more strongly indicated for other patients. Thus, the total cost to the health care system of ordering an unnecessary test may not be just financial, but rather may cause a patient who needs a test not to have it performed at an appropriate time. Adoption of a policy of appropriate (rather then redundant) utilization of health care resources by individual physicians could help assure that physicians, and not third party payers or government administrators, will contribute to the resolution of these issues.

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References

1. Kannel WB, Gordon T. The Framingham Study: An Epidemiologic Investigation of Cardiovascular Disease, Volume 12. Bethesda: National Heart, Lung, and Blood Institute, National Institutes of Health, 1968.
2. Coronary Risk Handbook. New York: American Heart Association, 1973.
3. Stamler J, Wentworth D, Naton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? JAMA 1986;256:2823–8.
4. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1981;305:799–807.
5. Patterson RE, Eng C, Horowitz SF. Practical diagnosis of coronary artery disease: a Bayes' theorem nomogram to correlate clinical data with noninvasive exercise tests. Am J Cardiol 1984;53:252–6.
6. Council on Scientific Affairs, American Medical Association. Indications and contraindications for exercise testing. JAMA 1981;246:1015.
7. Epstein SE, Palmeri S, Patterson RE. Evaluation of patients following acute myocardial infarction: indications for cardiac catheterization. N Engl J Med 1982:307:1487–92.
8. Takaro T, Hultgren, Detre KM, Peduzzi P. The Veterans Administration Cooperative Study of stable angina: current status. Circulation 1982; 65(Suppl II):II-60–7.

9. CASS Principal Investigators and Their Associates. Coronary Artery Surgery Study (CASS): a randomized trial of coronary artery bypass surgery: survival data. Circulation 1983;68:939–50.

10. Hurst JW, King SB, Walter PF, Friesinger GC, Edwards JE. Atherosclerotic coronary heart disease: angina pectoris, myocardial infarction, and other manifestations of myocardial ischemia. In: Hurst JW, Logue LB, Rackley CE, et al. eds. The Heart, Arteries and Veins. 5th ed. New York: McGraw-Hill, 1982:1009–149.

11. Cosgrove DM, Loop FD, Sheldon WC. Results of myocardial revascularization: a 12-year experience. Circulation 1982;65(suppl II):II-37–43.

12. Berger JH, Zaret B. Nuclear cardiology. N Engl J Med 1981;305:799–807.

13. Patterson RE, Horowitz SF, Eng C, et al. Can exercise electrocardiography and thallium-201 myocardial imaging exclude the diagnosis of coronary artery disease? Am J Cardiol 1982;49:1127–35.

14. Dash H, Massie BM, Botvinick EH, Brundage BH. The noninvasive identification of left main and three-vessel coronary artery disease by myocardial stress perfusion scintigraphy and treadmill exercise electrocardiography. Circulation 1979;60:276–84.

15. Patterson RE, Horowitz SF, Eng C, et al. Can noninvasive tests identify patients with left main or three vessel coronary disease after a first myocardial infarction? Am J Cardiol 1982;51:361–72.

16. Berger BC, Watson DD, Taylor GJ, Eller GA. Effect of coronary collateral circulation on regional myocardial perfusion assessed with quantitative thallium-201 scintigraphy. Am J Cardiol 1980;46:365–70.

17. Eng C, Patterson RE, Horowitz SF, et al. Functional collateral responses to exercise assessed by myocardial perfusion imaging. Circulation 1982:66:309–16.

18. McNeer JF, Margolis JR, Lee KL, et al. The role of exercise test in the evaluation of patients for ischemic heart disease. Circulation 1978;57:64–70.

19. Landenheim ML, Pollock BH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. J Am Coll Cardiol 1986;7:464–71.

20. Brown KA, Boucher CA, Okada RD, et al. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. J Am Coll Cardiol 1983;1:994–1001.

21. Gohlke H, Samek L, Betz P, Roskamm H. Exercise testing provides additional prognostic information in angiographically defined subgroups of patients with coronary artery disease. Circulation 1983;68:979–85.

22. Goldman ME, Horowitz SF, Blake J, et al. Can a specific pattern of exercise myocardial perfusion imaging predict prognosis? (abstr). J Am Coll Cardiol 1983:1:655.

23. Pryor DB, Harrell FE, Lee KL, et al. Prognostic indicators from radionuclide angiography in medically treated patients with coronary artery disease. Am J Cardiol 1984;53:18–22.

24. Bonow RO, Kent KM, Rosing DR, et al. Exercise-induced ischemia in mildly symptomatic patients with coronary artery disease and preserved left ventricular function: identification of subgroups at risk. N Engl J Med 1984;311:1339–45.

25. Marshall RC, Berger HJ, Costin JC, et al. Assessment of cardiac performance with quantitative radionuclide angiocardiography: sequential left ventricular ejection fraction, normalized left ventricular ejection rate, and regional wall motion. Circulation 1977;56:820–9.

26. Ritchie JL, Narahara KA, Trobaugh GB, Williams DL, Hamilton GW. Thallium-201 myocardial imaging before and after coronary revascularization: assessment of regional myocardial blood flow and graft patency. Circulation 1977;56:830–6.

27. Jones RH, Floyd RD, Austin EH, Sabiston DC. The role of radionuclide angiocardiography in the preoperative prediction of pain relief and prolonged survival following coronary artery bypass grafting. Ann Surg 1982;197:743–54.

28. Kent KM, Bonow RO, Rosing DR, et al. Improved myocardial function during exercise after successful percutaneous transluminal coronary angioplasty. N Engl J Med 1982;306:441–6.

29. Lusted LB. Introduction to Medical Decision-Making. Springfield, ILL: Charles C Thomas, 1968:1–46.

30. Feinstein AR. On the sensitivity, specificity and discrimination of diagnostic tests. In: Clinical Biostatistics. St. Louis: CV Mosby, 1977:214–28.

31. Metz CE. Basic principles of ROC analysis. Semin Nucl Med 1978;8:283–98.

32. Rifkin RD, Hood WB Jr. Bayesian analysis of electrocardiographic exercise stress testing. N Engl J Med 1977;207:681–6.

33. Hamilton GW, Trobaugh GB, Ritchie JL, Gould KL, DeRouen TA, Williams DL. Myocardial imaging with 201-thallium: an analysis of clinical usefulness based on Bayes' theorem. Semin Nucl Med 1978;7:758–64.

34. Cannon III RO, Bonow RO, Bacharach SL, et al. Left ventricular dysfunction in patients with angina pectoris, normal epicardial coronary arteries, and abnormal vasodilator reserve. Circulation 1985;71:218–25.

35. Rozanski A, Diamond GA, Forrester JS, Berman D, Morris D, Swan HJC. The declining specificity of exercise radionuclide angiocardiography. N Engl J Med 1983;309:518–22.

36. Fletcher RH, Fletcher SW, Wagner EH. Clinical Epidemiology: The Essentials. Baltimore: Williams & Wilkins, 1982:1–217.

37. Feinstein AR. The haze of Bayes', the aerial palaces of decision analysis, and the computerized Ouija board. Clin Pharmacol Ther 1979;21:482–95.

38. Weintraub WS, Maderia SW Jr, Bodenheimer MS, et al. Critical analysis of the application of Bayes' theorem to sequential testing in the noninvasive diagnosis of coronary artery disease. Am J Cardiol 1984;54:43–9.

39. Fryback DG. Bayes' theorem and conditional nonindependence of data in medical diagnosis. Comput Biomed Res 1978;11:423–31.

40. Diamond GA, Staniloff HM, Forrester JS, Pollock BH, Swan HJC. Computer-assisted diagnosis in the noninvasive evaluation of patients with suspected coronary artery disease. J Am Coll Cardiol 1983;1:444–55.

41. Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing: correlations among history of angina, ST-segment response and prevalence of coronary artery disease in the Coronary Artery Surgery Study (CASS). N Engl J Med 1979;301:230–5.

42. Hlatky MA, Pryor DB, Harrell FE, Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography: multivariable analysis. Am J Med 1984;77:64–71.

43. Diamond GA. Reverend Bayes' silent majority: an alternative factor affecting sensitivity and specificity of exercise electrocardiography. Am J Cardiol 1987;57:1175–80.

44. Cohn PF, Gorlin R, Vokonas PS, Williams RA, Herman MV. A quantitative clinical index for the diagnosis of symptomatic coronary artery disease. N Engl J Med 1972;286:901–9.

45. Pryor DB, Harrell FE, Lee KL, Califf RM, Rosati RA. Estimating the likelihood of significant coronary artery disease. Am J Med 1983;75:771–80.

46. Diamond GA, Forrester JS. Metadiagnosis: an epistomologic model of clinical judgement. Am J Med 1984;75:129–37.

47. Patterson RE, Eng C, Horowitz SF, Gorlin R, Goldstein SR. Bayesian comparison of cost-effectiveness of different clinical approaches to diagnose coronary artery disease. J Am Coll Cardiol 1984;4:278–89.

48. Berger HJ, Eisner RL, DePuey EG, Patterson RE. New vistas in cardiovascular nuclear medicine. J Nucl Med 1985;25:1254–8.